# Chronic Fatigue Syndrome

## Information for Physicians

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**NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES**
**NATIONAL INSTITUTES OF HEALTH**
PUBLIC HEALTH SERVICE
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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# Introduction

Chronic fatigue syndrome (CFS) is an illness characterized by prolonged, debilitating fatigue and multiple nonspecific symptoms such as headaches, recurrent sore throats, muscle and joint pains, and cognitive complaints. Profound fatigue, the hallmark of the disorder, can come on suddenly or gradually and persists or recurs throughout the period of illness. Unlike the short-term disability of an acute infection, CFS symptoms by definition linger for at least 6 months and often for years.

An estimated one-quarter of all patients seeing general practitioners complain of prolonged fatigue, a symptom common to many illnesses. Several studies indicate that only a small fraction of these patients meet the criteria for *chronic fatigue syndrome.*

To identify people with CFS, physicians can evaluate patients with persistent fatigue of undetermined cause using the CFS definition in the appendix as a guide. This description, developed by the International CFS Study Group and published in the *Annals of Internal Medicine* in December 1994, replaces the first research case definition published 6 years earlier. The revised, more inclusive criteria define CFS and other cases of unexplained prolonged fatigue, suggest how to further subdivide these groups for research studies, and include guidelines for nonresearch clinicians as well. The case criteria will continue to be reviewed and refined as new information warrants.

Despite multidisciplinary investigations into the cause of CFS, its etiology remains unknown. Similarly, no specific diagnostic tests or therapies for CFS exist. A supportive program of patient management—including symptom-based treatment, education about the disease, and regular followup visits to rule out alternative diagnoses—can offer reassurance, dispel unfounded beliefs about CFS or its treatment, and help patients and their families adjust to living with this chronic illness.

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# Historical Perspective

CFS does not appear to be a new illness. Relatively small outbreaks of similar disorders have been described in the medical literature since the 1930s. Furthermore, case reports of comparable illnesses date back several centuries, some possibly linked to bacterial, viral, or protozoal infections such as brucellosis, yellow fever, hepatitis, influenza, and malaria.

Fatigue syndromes also have been long recognized outside the setting of an infectious illness. For example, the clinical descriptions of CFS and the rheumatologic disorder fibromyalgia, first described in the 19th century, overlap considerably. CFS and depression also share some symptoms.

Interest in what now is called CFS was renewed in the mid-1980s after several studies found slightly higher levels of antibody to Epstein-Barr virus (EBV) in patients with

CFS-like symptoms than in healthy individuals. Most of these patients had experienced an episode of infectious mononucleosis a few years before the onset of their new chronic, debilitating illness. As a result, for a time the CFS-like illness became popularly termed "chronic EBV."

*Chronic EBV is an inappropriate label for this illness and should be abandoned.*

In subsequent investigations, it became clear that elevated EBV antibody titers were not diagnostic for CFS: Some healthy people have high EBV titers and some people with CFS do not. Currently, it is not considered useful to test for antibodies to EBV in a patient with symptoms suggestive of CFS. More than 90 percent of adults in developed countries have been exposed to EBV by age 30, and moderately elevated antibody titers have not been associated with any EBV-related disease. Chronic EBV is an inappropriate label for this illness and should be abandoned.

The name "chronic fatigue syndrome," chosen because it reflects the most common symptom, was selected for the illness by a group of experts in 1988. When the International CFS Study Group updated the case definition, they decided to retain this name until the discovery of a specific cause of or marker for the illness suggests a more fitting name.

Symptom complexes similar to CFS also are known as epidemic neuromyasthenia, myalgic encephalomyelitis, postviral fatigue syndrome, and chronic fatigue and immune dysfunction syndrome in different parts of the world. No immune dysfunction specific to CFS has been found, however, and there is no evidence linking encephalomyelitis to the pathology of the illness.

## Epidemiology

Most CFS cases are sporadic. No published data indicate that CFS is contagious, that it can be transmitted through intimate or casual contact or by blood transfusion, or that people with CFS need to be isolated in any way.

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Occasionally, close contacts, including family members, become ill with CFS at about the same time. Also, clusters of CFS-like illnesses have been reported during the past 60 years in various families, communities, or workplaces. Outbreaks of CFS are unusual, however, and have proven difficult to validate. Case clusters should be reported to state health officials for investigation.

Although the typical patient seeking medical care for CFS is a Caucasian woman between her mid-twenties and late forties, patients of both sexes across a wide range of ages, races, and socioeconomic groups have been affected. The demographics of the population currently diagnosed with CFS may be biased by cultural differences and access to medical care, an issue addressed in the design of more recent epidemiologic surveys.

Without objective diagnostic criteria, the prevalence of CFS is difficult to measure. The Centers for Disease Control and Prevention (CDC) estimates the minimum CFS

prevalence rate in the United States is 4 to 10 cases per 100,000 adults 18 years of age or older (based on physician-referred patients from four cities evaluated by the 1988 case definition and adjusted for age, sex, and race). A several-fold higher prevalence rate of self-reported *CFS-like* illness exists according to preliminary, unpublished results from a 17,000-person survey coordinated by CDC in an unreferred San Francisco population, and to independent findings of smaller community-based surveys. However, in the CDC survey most CFS-like illness appeared to be due to other causes. When these people were evaluated by a physician, the rate of illness consistent with the 1988 CFS case definition was approximately twice that identified by the physician-referred study. This experience underscores the importance of physician evaluation to rule out other, potentially treatable illnesses.

The usefulness of the case definition in pediatric populations in the United States is currently being evaluated. Recent CDC studies indicate that the prevalence rate in adolescents is slightly lower than that in adults. Cases in children under 12 years old appear to be much less common.

Outside the United States, CFS and CFS-like syndromes have been reported widely, including in Europe, Australia, New Zealand, Canada, Iceland, Japan, Russia, and South Africa.

# Clinical Picture

CFS often begins abruptly, but sometimes the onset is gradual. In about one-third of cases, the sudden onset follows a respiratory, gastrointestinal, or other acute infection with flu-like symptoms, including mononucleosis. Other cases develop after emotional or physical traumas such as bereavement or surgery.

***In about one-third of cases, the sudden onset follows a respiratory, gastrointestinal, or other acute infection with flu-like symptoms, including mononucleosis.***

Besides a debilitating fatigue unrestored by rest, common symptoms of CFS include more intense or changed patterns of headaches; reduced short-term memory or concentration; recurrent sore throats; tender lymph nodes; muscle discomfort or pain; joint pain without joint swelling or redness; unrefreshing sleep; and postexertional malaise lasting more than 24 hours (table 1; see appendix for detailed list). The severity of CFS symptoms varies broadly among individuals.

A majority of CFS patients also report mild to moderate symptoms of anxiety or depression. Several studies report a high rate of coexisting psychiatric diagnoses in CFS patients, greater than that found in patients with other debilitating medical illnesses such as rheumatoid arthritis, multiple sclerosis, and neuromuscular disease. It is important to note, however, that about 20 to 40 percent of carefully evaluated CFS patients do not have depression or another psychiatric illness.

Some studies have found a significantly greater prevalence of allergy in CFS patients than in the general population. Many CFS patients have a history of allergies years before the onset of the syndrome. Sometimes patients report a worsening of allergic symptoms or the onset of new allergies after becoming ill with CFS. Because allergies

## Table 1. Clinical Evaluation and Classification of Chronic Fatigue

I. Clinically evaluate cases of chronic fatigue by:
   A. History and physical examination
   B. Mental status examination (abnormalities require appropriate psychiatric, psychologic, or neurologic examination)
   C. Tests (abnormal results that strongly suggest an exclusionary condition must be resolved)
      1. Screening lab tests: complete blood count, erythrocyte sedimentation rate, alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, creatinine, thyroid stimulating hormone, and urinalysis
      2. Additional tests as clinically indicated to exclude other diagnoses.

→ Exclude if another cause for chronic fatigue is found.

II. Classify as either chronic fatigue syndrome or idiopathic chronic fatigue.

A. Classify as chronic fatigue syndrome if both of the following criteria are met:
   1. Unexplained persistent or relapsing fatigue of new or definite onset that is not due to ongoing exertion, is not relieved by rest, and results in a substantial reduction in previous levels of activity
   2. Four or more of the following symptoms are concurrently present for 6 months or longer:
      a) impaired memory or concentration*
      b) sore throat
      c) tender cervical or axillary lymph nodes
      d) muscle pain
      e) multijoint pain†
      f) new headaches
      g) unrefreshing sleep
      h) postexertion malaise.‡

B. Classify as idiopathic chronic fatigue if fatigue severity or symptom criteria for chronic fatigue syndrome are not met.

III. Subgroup research cases by the presence or absence of the following essential parameters:
   A. Comorbid conditions (psychiatric conditions must be documented by use of an instrument)
   B. Current level of fatigue (measured by a scale)
   C. Duration of fatigue
   D. Current level of physical function (measured by an instrument).

Subgroup research cases further as needed by optional parameters such as epidemiologic or laboratory features of interest.

* severe enough to reduce levels of occupational, social, or personal activities
† without joint swelling or redness
‡ lasting more than 24 hours
Adapted from Fig.2, K Fukuda et al, *Ann Int Med* 121: 953-9 (1994).

are so common in people with CFS, it is important to differentiate those symptoms that are allergy-related and thus amenable to specific therapies.

Although CFS can persist for many years, longitudinal and followup studies indicate that CFS generally is not a progressive illness. The symptoms usually are most severe in the first year or two. Thereafter, the symptoms typically stabilize and then persist chronically, wax and wane, or improve. Most patients partially recover, some fully recover, and others recover and relapse. Currently, an individual's course of illness cannot be predicted. No long-term health risks, such as an increased risk of cancer, have been associated with having CFS.

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## Immunologic features

Various immunologic findings have been described in patients with CFS, but no single immunologic disturbance has been reported consistently or yet been identified as typical of the syndrome, nor have these findings correlated with symptoms or prognosis. The disturbances include depressed natural killer (NK) cell activity, modest increases in the number of circulating lymphocytes that appear to be activated, and slightly elevated levels of circulating immune complexes. All of these findings point to general differences between patient populations and control groups, but none is specific for CFS or abnormal in all CFS patients. In addition, immunologic changes like these often accompany various infections as well as physically or emotionally stressful experiences. The character, epidemiology, and prognosis of CFS also are distinct from those of major immune deficiency disorders, including acquired immunodeficiency syndrome (AIDS): For example, there is no published evidence that CFS is associated with opportunistic infections or an increased risk for the development of malignancies.

## Neuropsychologic features

For many patients, the cognitive impairment they experience is one of the most debilitating and disconcerting symptoms. CFS patients do not exhibit gross dementia, but most often report an inability to concentrate, unusual forgetfulness, and difficulty with information processing and word finding. CFS patients often subjectively report worse cognitive problems than are indicated by objective evidence obtained with formal testing. Whether this discrepancy reflects some distortion in perceived symptoms on the part of the patient or a deficiency in test methodology is unresolved at this time. Although most controlled studies have found no significant and reproducible neuropsychologic abnormalities in CFS patients, research provides some evidence that a subset of CFS patients have deficits in complex auditory cognitive processing.

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Some CFS patients report other neurologic symptoms, including paresthesias, disequilibrium, and visual blurring. These usually are not accompanied by any evidence of gross or localized neurologic signs.

Some studies using magnetic resonance imaging (MRI) or SPECT scanning have found brain abnormalities associated with CFS while others have not. The positive reports are preliminary and unconfirmed. The abnormalities are neither detected consistently nor are they specific to the syndrome. The use of MRI, SPECT scans, or other neuroimaging techniques in CFS patients cannot be justified at this time unless the differential diagnosis indicates otherwise.

**Table 2.**
**Some Conditions That Can Explain Chronic Fatigue**

- Hypothyroidism
- Sleep apnea
- Narcolepsy
- Unresolved hepatitis B or C
- Alcohol or substance abuse
- Severe obesity
- Iatrogenic, e.g. medication side effects
- Systemic lupus erythematosus
- Multiple sclerosis
- Cancer
- Major depressive disorder
- Anorexia nervosa
- Bulimia nervosa
- Schizophrenia
- Bipolar disorder
- Dementia

# Evaluation of Patients

The patient reporting that chronic fatigue is interfering with his or her life should be treated with compassion and evaluated carefully. Because people with CFS usually do not look as sick as they feel, family members, friends, employers, and physicians may doubt the patient's claim of illness.

The diagnosis of CFS is primarily one of exclusion. Table 2 lists some conditions that should be considered and ruled out as alternative explanations for presenting symptoms in patients with chronic fatigue. This list may be useful but is not exhaustive. (See appendix for further details.)

CFS symptoms overlap with those of fibromyalgia, Lyme borreliosis, mild systemic lupus erythematosus (SLE), early or mild multiple sclerosis (MS), depression, and numerous other well-recognized disorders.

CFS and fibromyalgia, closely related illnesses, commonly coexist in the same patient. The diagnosis of fibromyalgia, however, unlike that of CFS, requires the detection of discrete tender points. Also, the typical fibromyalgia patient may be slightly older and have more widespread soft-tissue pain. A diagnosis of fibromyalgia does not exclude one of CFS, but when analyzing data from research studies, CFS patients with this disorder should be subgrouped.

A history of possible tick exposure, the typical Lyme rash (erythema chronicum migrans), and antibodies to *Borrelia burgdorferi* suggest the diagnosis of Lyme disease. It has recently been recognized, however, that *B. burgdorferi* can trigger CFS in some people who have received adequate treatment for Lyme disease, are refractory to further antibiotic treatment, and have no evidence of persisting infection with the spirochete.

In other illnesses like SLE and MS, debilitating chronic fatigue can be more prominent than rheumatologic or neurologic symptoms, but the presence of objective physical findings, laboratory abnormalities, and illness progression point to the correct diagnosis.

Psychiatric illnesses that most resemble CFS include major depressive episode, panic disorder, generalized anxiety disorder, and somatization disorder. Because subtle psychiatric problems can be difficult to recognize, consultation with a psychiatrist or psychologist may benefit the evaluation and management of some patients. The relationship between

psychiatric illness and CFS is complex, interactive, and not yet well understood. For this reason, a history of prior or current depressive episodes does not exclude a diagnosis of CFS, but the revised CFS case definition recommends stratifying these patients when analyzing data for research purposes. For the case definition, a history of major depression with psychotic or melancholic features, bipolar affective disorder, schizophrenia, delusional disorder, dementia, active substance or alcohol abuse, anorexia nervosa, or bulimia excludes a diagnosis of CFS because these illnesses preclude the reliable determination of the core symptoms of CFS.

A reasonable initial laboratory workup is listed in table 3. Significantly abnormal results on any of these tests should prompt consideration of other medical diagnoses. It is also prudent to consider the possibility of infection with the human immunodeficiency virus (HIV). Subsequent workup should be guided by the clinical picture. The patient's medical history—particularly usage of prescription and over-the-counter drugs, including vitamins and supplements—a complete physical examination, and a mental status examination to screen for any major abnormalities will help determine the need for more laboratory tests.

**Table 3. Initial Laboratory Workup**

| |
|---|
| Urinalysis |
| Complete blood count with differential |
| Chemistry panel |
| Thyroid function test (TSH may suffice) |
| Erythrocyte sedimentation rate |
| Alanine aminotransferase |
| Total protein |
| Albumin |
| Globulin |
| Alkaline phosphatase |
| Calcium |
| Phosphorus |
| Glucose |

### Children and adolescents

The presentation of CFS in children and adolescents is similar to that in adults but is less well studied. A supportive approach can help reduce the anxiety of young patients and their families during the evaluation period. CFS can be difficult to diagnose in younger children who have trouble describing illness symptoms and articulating their concerns, leaving the parents to recount their perceptions of their child's medical history. As for any chronic illness in a child, it is important to direct careful attention to family functioning to identify and address underlying family problems or psychopathology that may be contributing to the CFS-like symptoms. Age-appropriate tests must be used, as needed, to assess stress, depression, and anxiety.

The physician should be prudent in applying the diagnostic label CFS to a young person. In the event that the symptoms are misdiagnosed as CFS, the potential consequences of not providing the proper treatment or of possibly perpetuating inappropriate illness behaviors—especially the effects on psychosocial development and identity—may be even more profound than in an adult. It is essential to schedule regular followup visits to offer reassurance, make adjustments in treatments, and note any changes that could indicate another source of the symptoms.

## Patient Management

CFS is debilitating in all patients, disabling in some, but usually not progressive. The debility and disability stem from a combination of symptoms such as fatigue, muscle and joint pain, sleep disturbances, cognitive impairment, and, in some patients, from associated depression. Patients need both symptomatic treatment and emotional support (see table 4).

**Table 4. Elements in CFS Patient Management**

| |
|---|
| Establish therapeutic alliance with patient |
| Dispel misinformation about the disease |
| Use a medical team approach |
| Prescribe symptomatic treatments |
| Urge stress reduction |
| Introduce slowly graduated exercise |
| Suggest rehabilitation therapy to develop energy conservation techniques |
| Schedule regular followup visits |
| Give emotional support |

It is vitally important for the physician to be the patient's advocate. Forging a therapeutic alliance based on trust and open exchange can counter misinformation about the disease. In the absence of any proven treatments, carefully selected empiric therapies should be tried. At the same time, patients need to be cautioned to avoid using exotic, untested remedies that may be harmful. Physicians should continually be on the lookout for other medical problems and avoid the assumption that every new sign or symptom is a manifestation of CFS. It is common practice to schedule followup visits every 6 months or whenever there is a disconcerting new finding or complaint.

It is important for people with CFS to slow the pace of their lives, and avoid or reduce their exposure to situations that are physically or psychologically stressful. Having a chronic illness is stressful in itself. Counseling can help both the patient and his or her family adjust to the uncertain course of the illness and its effects on roles and relationships in and outside the family. Some patients benefit from participation in CFS support groups. The patient and the family need to realize that no definitive diagnostic or therapeutic approaches exist and no specific nutritional program has proved valuable, although a balanced diet and rest generally enhance well-being. Referrals to professionals who can help patients with practical matters, such as applying for disability and obtaining home health care, if needed, can help some patients and their families better manage this illness.

Psychiatric problems need to be actively considered and treated. Ideally, the psychiatrist should have experience in treating patients with CFS or related chronic illnesses and should become part of the medical care team, if possible, to reassure the patient that he or she is not just being passed on to another specialist. Recent data also indicate that cognitive behavioral therapy may improve disability and symptoms in some patients whose coping behaviors or perceptions of their illness inhibit their recovery.

Patients should receive guidance about how to balance activity and rest, to set realistic goals, to create flexible plans to account for fluctuations in energy and symptoms, and to remain optimistic about recovery. Referral to an occupational therapist who can design strategies for conserving energy and, if appropriate, to a vocational rehabilitation therapist, may help CFS patients improve their functional capacity, limit deconditioning, and enhance their lives, even if their symptoms remain the same.

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Abrupt resumption of exercise usually exacerbates symptoms and should be avoided. At a minimum, however, patients should be encouraged to engage in any form of gradually reintroduced physical activity to tolerance. A slowly graduated exercise program tailored to the individual—if warranted, through an ongoing program of physical therapy—can build confidence in the patient that some level of physical conditioning can be achieved.

For children and adolescents, the physician should work with the school to limit class time, if necessary, and to resume normal attendance gradually. Home tutoring may be an alternative.

## Drug treatment

Although there is no one drug or group of drugs specific for CFS, symptomatic treatment is helpful. To reduce the muscle and joint pains, headaches, or feelings of feverishness associated with the illness, aspirin, other nonsteroidal anti-inflammatory drugs, or acetaminophen may be prescribed. Nonsedating antihistamines may help relieve any prominent allergic symptoms.

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Double-blind, placebo-controlled CFS therapy trials have found no or limited utility for most other drugs tested. The first such trial reported found the antiviral drug acyclovir to be no better than placebo, with a large portion of the patients on placebo reporting improvement. Although some physicians prescribe intramuscular or intravenous gamma globulin, three controlled clinical trials of intravenous immunoglobulin have yielded conflicting results regarding efficacy. Despite the high prevalence of allergies in the CFS population, a trial of terfenadine found no benefit for patients with CFS. One placebo-controlled trial of essential fatty acids found some efficacy while another did not. Injectable liver extract also did not appear to be effective in controlled clinical trials.

Recently, a strong link between CFS and neurally mediated hypotension was reported. The study found that 22 of 23 CFS patients tested positive for neurally mediated hypotension by specialized tilt-table testing and pharmacologic provocation. Of those who tested positive, 16 reported full or partial recovery from fatigue after uncontrolled treatment with fludrocortisone, beta-adrenergic blocking agents, and disopyramide, alone or in combination. A randomized, placebo-controlled study is under way to attempt to validate these preliminary results.

Several additional empiric therapies have been tried for CFS. Because well-designed clinical trials have demonstrated the benefit of low doses of tricyclic antidepressant drugs in fibromyalgia, tricyclics such as amitriptyline, desipramine, doxepin, and nortriptyline are widely prescribed for CFS patients. Anecdotal experience with tricyclics and selective serotonin reuptake inhibitors (SSRIs) generally has been positive. Besides targeting depression, some antidepressants appear to act by improving the quality of sleep and/or decreasing pain. However, CFS patients often report that antidepressants given in full, therapeutic doses exacerbate their fatigue. It may be necessary to escalate doses very slowly and urge patience in detecting benefit, or to try the more activating antidepressants such as desipramine, SSRIs such as fluoxetine and sertraline, or monamine oxidase inhibitors. Many CFS patients are extremely sensitive to these drugs, and it is common practice to start a patient at one-tenth to one-quarter of the usual clinical dose.

Although adequate controlled trials are lacking, some CFS patients who also suffer from panic disorder or anxiety have reported benefit from anxiolytic medications such as alprazolam, clonazepam, other benzodiazepines, or buspirone.

Because no specific regimen for treating CFS exists, several different treatment approaches may have to be tried before the patient reports benefit. Both the physician and the patient need to be open to reasonable treatment options and appreciate that improvement may occur in small increments.

# Etiologic Theories

The etiology of CFS continues to be vigorously investigated. Because of the syndrome's heterogeneity, many researchers argue against it being a discrete disease caused by one agent. For example, although some CFS patients exhibit any of a variety of immunologic disturbances, no single pattern of disturbances appears consistently, and many patients test in the normal range. Sometimes the syndrome appears to follow an infection or physical or psychological trauma, but cases also develop gradually without an obvious triggering event. Higher-than-normal antibody levels to a variety of viruses appear in some but not all patients. Finally, although many people with CFS suffer from anxiety or depression, which may or may not predate their CFS, about one-third of CFS patients do not have a psychiatric illness.

Instead of a discrete disease, many researchers believe CFS represents a common set of symptoms triggered by different combinations of various infectious and noninfectious factors. This idea is consonant with a model proposing that, like hypertension or anemia, CFS be considered a clinical condition.

## Infectious Agents

Despite extensive efforts by many laboratories, no published data implicate a specific virus or other microbe as the cause of CFS. Several efforts to confirm initial reports that novel retroviruses or a spumavirus might be involved in CFS also have been unsuccessful. Known or newly discovered viruses continue to be investigated as possible factors in causing the illness or influencing its course.

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It appears likely, however, that infectious agents, among other stressors, can precipitate the syndrome. The best evidence comes from carefully studied cases of new infection with *B. burgdorferi*, in which CFS was triggered following apparent resolution of the bacterial infection.

A variety of common viruses can be reactivated in some CFS patients, including the herpesviruses EBV, cytomegalovirus, herpes simplex virus 1 and 2, and human herpesvirus 6. Most investigators believe virus reactivation could be occurring secondarily to some immunologic disturbance. No direct evidence links any of these viruses, or enteroviruses such as coxsackievirus and echovirus, to the cause of CFS or its symptoms.

## Immunologic theories

Other theories of CFS etiology focus on the immune system. One theory postulates that the illness involves a constant antigenic challenge to the immune system and, as a consequence, a constant immunologic response to that challenge. A related idea suggests that after controlling or eliminating the antigen involved in the acute, precipitating disease, the immune system remains in high gear instead of returning to normal. According to these ideas, the immune system produces excess levels of inflammatory mediators and cytokines, such as interleukins and interferons, which trigger the flu-like symptoms of CFS. However, consistent evidence of abnormal cytokine levels in CFS patients has not been found.

## Central nervous system model

The central nervous system figures prominently in other theories of CFS etiology that try to unify the disparate biological and clinical features of the syndrome. According to one such theory, the interaction between various events (for example, infectious agents, physical or emotional stress, environmental exposures, genetics, and psychiatric history) prior to the onset of the syndrome ultimately converge in a clinical condition that is perpetuated by a specific pathologic response to those events. This pathologic response may represent a disruption of a common biologic pathway coordinated by the central nervous system.

*CFS patients as a group were found to have a subtle deficiency of the stress hormone cortisol, the opposite of the hypercortisolism that characterizes melancholic depression....*

Supporting this theory is the finding of a confirmed, well-controlled neuroendocrine study. CFS patients as a group were found to have a subtle deficiency of the stress hormone cortisol, the opposite of the hypercortisolism that characterizes melancholic depression, one of the most common subtypes of major depression. Not only do these observations suggest that disturbances in the hypothalamic-pituitary-adrenal (HPA) axis play a role in both syndromes, the results attest to the biologic distinctions between CFS and a principal form of major depression while offering one possible explanation for their overlapping clinical presentations. Because cortisol is a potent suppressor of immune responses, this finding also may explain the immune disturbances seen in some people with CFS. Hypocortisolism also has been reported in patients with fibromyalgia, an illness strikingly similar to CFS.

Although researchers have just begun to explore at the molecular level the interactions between stress, the neuroendocrine system, and the immune response, this is an active area of research.

Recently reported preliminary research also suggests considerable overlap between CFS and neurally mediated hypotension, a potentially treatable illness (see p. 9). This finding is consistent with the neuroendocrine abnormality described above and, if confirmed, would support the theory that CFS is a multisystem illness with prominent CNS involvement.

# Conclusion

A great deal of controversy and speculation surrounds CFS: Is it a single disorder or a heterogeneous mix of problems? What is its relationship to infections, to the immune system, to neurally mediated hypotension, and to mood disturbances? How can it best be treated? These and many more issues fuel the continuing broad debate, often leaving patients and their physicians frustrated. For now, neither physicians nor researchers have all the answers. But in treating people with CFS, physicians can draw on practices that have always made medicine a valued art: exclude alternative problems, ameliorate symptoms, and offer guidance with compassion.

# Appendix

## Guidelines for the Clinical Evaluation of the Chronic Fatigue Syndrome and Other Illnesses Associated with Unexplained Chronic Fatigue*

Prolonged fatigue is defined as self-reported, persistent fatigue lasting 1 month or longer. Chronic fatigue is defined as self-reported persistent or relapsing fatigue lasting 6 or more consecutive months.

The presence of prolonged or chronic fatigue requires clinical evaluation to identify underlying or contributing conditions that require treatment. Further diagnosis or classification of chronic fatigue cases cannot be made without such an evaluation. The following items should be included in the clinical evaluation.

1. A thorough history that covers medical and psychosocial circumstances at the onset of fatigue; depression or other psychiatric disorders; episodes of medically unexplained symptoms; alcohol or other substance abuse; and current use of prescription and over-the-counter medications and food supplements.

2. A mental status examination to identify abnormalities in mood, intellectual function, memory, and personality. Particular attention should be directed toward current symptoms of depression or anxiety, self-destructive thoughts, and observable signs such as psychomotor retardation. Evidence of a psychiatric or neurologic disorder requires that an appropriate psychiatric, psychological, or neurologic evaluation be done.

3. A thorough physical examination.

4. A minimum battery of laboratory screening tests including complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis.

Routinely doing other screening tests for all patients has no known value. However, further tests may be indicated on an individual basis to confirm or exclude another diagnosis, such as multiple sclerosis. In these cases, additional tests or procedures should be done according to accepted clinical standards.

The use of tests to diagnose the chronic fatigue syndrome (rather than to exclude other diagnostic possibilities) should be done only in the setting of protocol-based research. The fact that such tests are investigational and do not aid in diagnosis or management should be explained to the patient.

* Excerpted and reprinted with permission from K Fukuda et al. The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study. *Ann Int Med* 121:953-9 (1994).

In clinical practice, no additional tests, including laboratory tests and neuroimaging studies, can be recommended for the specific purpose of diagnosing the chronic fatigue syndrome, including serologic tests for Epstein-Barr virus, retroviruses, human herpesvirus 6, enteroviruses, and *Candida albicans*; tests of immunologic function, including cell population and function studies; and imaging studies, including magnetic resonance imaging scans and radionuclide scans (such as single-photon emission computed tomography and positron emission tomography) of the head.

### *Conditions That Explain Chronic Fatigue*

The following conditions exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnea, and narcolepsy, and iatrogenic conditions such as side effects of medications.

2. Any previously diagnosed medical condition whose resolution has not been documented beyond reasonable clinical doubt and whose continued activity may explain the chronic fatiguing illness. Such conditions may include previously treated malignancies and unresolved cases of hepatitis B or C virus infection.

3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype, anorexia nervosa, or bulimia nervosa.

4. Alcohol or other substance abuse within 2 years before the onset of the chronic fatigue and at any time afterward.

5. Severe obesity as defined by a body mass index [body mass index = weight in kilograms/(height in meters)$^2$ equal to or greater than 45].

Any unexplained physical examination finding or laboratory or imaging test abnormality that strongly suggests the presence of an exclusionary condition must be resolved before further classification.

### *Conditions That Do Not Adequately Explain Chronic Fatigue*

The following conditions do not exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.

3. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptomatic sequelae.

4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate to strongly support a diagnosis of a discrete connective tissue disorder without other laboratory or clinical evidence.

### *Major Classification Categories: Chronic Fatigue Syndrome and Idiopathic Chronic Fatigue*

Clinically evaluated, unexplained cases of chronic fatigue can be separated into either the chronic fatigue syndrome or idiopathic chronic fatigue on the basis of the following criteria.

A case of the chronic fatigue syndrome is defined by the presence of the following:

1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and 2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain, multijoint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours.

The method used (for example, a predetermined checklist developed by the investigator or spontaneous reporting by the study participant) to establish the presence of these and any other symptoms should be specified.

A case of idiopathic chronic fatigue is defined as clinically evaluated, unexplained chronic fatigue that fails to meet criteria for the chronic fatigue syndrome. The reasons for failing to meet the criteria should be specified.

# Public Health Service Resources

## Selected CFS Reviews

K Fukuda et al. The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study. *Annals of Internal Medicine* 121:953-9 (1994).

K Fukuda and NM Gantz. Management Strategies for Chronic Fatigue Syndrome. *Federal Practitioner* 12:12-7 (1995).

AC Mawle, M Reyes, and DS Schmid. Is Chronic Fatigue Syndrome an Infectious Disease? *Infectious Agents and Disease* 2:333-41 (1994).

R McKenzie and SE Straus. Chronic Fatigue Syndrome. *Advances in Internal Medicine* 40:119-53 (1995).

SE Straus, ed. *Chronic Fatigue Syndrome*. Marcel Dekker, Inc. New York, 1994.

*The Facts About Chronic Fatigue Syndrome*. CDC. Atlanta, March 1995.

## World Wide Web Sites With CFS Information

National Institute of Allergy and Infectious Diseases
*http://www.niaid.nih.gov*

Centers for Disease Control and Prevention
*http://www.cdc.gov*

## American Association for Chronic Fatigue Syndrome

AACFS is a membership organization for clinicians as well as research and health care workers professionally engaged in CFS activities. Information about the organization can be accessed 1) from the Web site listed below, 2) by phoning 1-800-232-8710 or 518-435-1765, or 3) by writing to AACFS, 7 Van Buren St., Albany, NY 12206.

An extensive CFS bibliography can be found at the AACFS World Wide Web site
*http://weber.u.washington.edu/~dedra/aacfs1.html*

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